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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/816,768	04/02/2004	Hermann Oppermann	STK-075 CON	3980

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EXAMINER	
LI, RUIXIANG	
ART UNIT	PAPER NUMBER
1646	
MAIL DATE	DELIVERY MODE
01/14/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/816,768	OPPERMANN ET AL.	
	Examiner	Art Unit	
	RUIXIANG LI	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *1-5 and 10-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6-9, 20, and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, and/or Claims

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 12/22/2008 has been entered. Claims 1-21 are pending. Claims 6-9, 20, and 21 are currently under consideration. All other claims are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Withdrawn Objections and/or Rejections

The disclosure is objected to because it refers to the Atty Docket No. is withdrawn in view of amended specification.

The rejection of claims 6-9, 20, and 21 under 35 U.S.C. 112, second paragraph is withdrawn in view of Applicants' argument.

The rejection of claims 6-9, 20, and 21 under 35 U.S.C. 112, first paragraph for new matter is withdrawn in view of Applicants' argument.

Objection to the Specification

The disclosure is objected to because the specification discloses that a modified morphogen containing a collagen binding domain (e.g., H2487, shown in Figure 7A) can be delivered in an inactive form to a desired tissue locus (e.g., a locus containing an implanted collagen matrix) and cleaved at that locus to produce an active morphogen (at page 79, the 2nd paragraph). However, the specification also discloses that a fusion protein of H2487 comprising a collagen-binding domain and modified OP-1 was successfully refolded and active in the ROS assay (page 77, lines 16-20), contradicting to the disclosure at page 79, the 2nd paragraph of the specification. Appropriate correction is required.

Claim Rejections under 35 USC § 112, 1st paragraph

(i). The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

(ii). Claims 6-9, 20, and 21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the latent fusion proteins, H2440 and H2487, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/ or use the invention commensurate in scope with these claims.

The factors that are considered when determining whether a disclosure satisfies enablement requirement include: (i) the quantity of experimentation necessary; (ii) the

amount of direction or guidance presented; (iii) the existence of working examples; (iv) the nature of the invention; (v) the state of the prior art; (vi) the relative skill of those in the art; (vii) the predictability or unpredictability of the art; and (viii) the breadth of the claims. *Ex Parte Forman*, 230 USPQ 546 (Bd Pat. App. & Int. 1986); *In re Wands*, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988).

Claim 6 is drawn to a latent TGF-β family member fusion protein, comprising a first TGF-β family proein C-terminal seven cysteine domain, comprising a finger 1 subdomain, a finger 2 subdomain, and a heel subdomain; and a cleavable leader sequence operably linked to said C-terminal domain wherein said cleavable leader sequence is selected from the group consisting of a leader sequence derived from a second TGF-β family protein, a metal-binding domain, a protein-binding domain, a ceramic-binding domain, a hydroxyapatite-binding domain and a collagen-binding domain; wherein said cleavable leader sequence inhibits the biological activity associated with said C-terminal domain; wherein said C-terminal domain becomes active upon cleavage of a part or all of said leader sequence; and wherein said latent protein is a refolded protein. Claims 7-9, 20, and 21 depend from claim 16. Thus, the claims encompass a genus of cleavable sequences operably linked to a genus of TGF-β family protein C-terminal domains.

The specification discloses a fusion protein, H2440, which is a hexa-his tagged OP-1 (Fig. 7B). This protein was purified over copper IMAC resin, initially in its unfolded state,

in the presence of urea. The folded fusion protein displayed little or no activity in a ROS assay, but was activated upon cleavage of the N-terminal non-morphogen peptide to yield an active C-terminal morphogen domain (page 77, the 1st paragraph). The specification also discloses that a modified morphogen containing a collagen binding domain (H2487, shown in Figure 7A) can be delivered in an inactive form to a desired tissue locus (e.g., a locus containing an implanted collagen matrix) and cleaved at that locus to produce an active morphogen (at page 79, the 2nd paragraph). However, the specification also states that the fusion protein of H2487 was successfully refolded and active in the ROS assay (page 77, lines 16-20), contradicting to the above disclosure at page 79, the 2nd paragraph of the specification. While the specification discloses numerous lead sequences that can be used to make a fusion protein (page 77, lines 7-8), the specification fails to provide sufficient guidance and/or working examples with respect to how to make any other latent TGF-β family member fusion proteins, such as a latent fusion protein comprising a first TGF-β family protein C-terminal domain and a leader sequence derived from a second TGF-β family protein, or a fusion TGF-β family protein wherein a part of the leader sequence is cleaved.

While disclosing that some N-terminal fusion protein monomers disclosed in the instant disclosure do not form active homodimers without cleavage of the leader sequence (page 79, last paragraph), the specification does not provide description of the structural feature that makes a leader sequence inhibits the biological activity associated with a TGF-β family protein C-terminal domain and thus renders a TGF-β family member

fusion protein latent. It is unpredictable whether a given TGF-β family protein comprising a leader sequence is a latent fusion protein.

The prior art teaches that the activities of the refolded proteins depend upon the refolding conditions (Hall et al., WO 96/39430, 12 December 1996; Nimni et al., U.S. Patent No. 6,352,972 B1). For example, Hall et al. teach that the refolded fusion protein comprising a His-tagged C-terminal active fragment of TGFβ1 under low concentrations of urea and DTT or a redox system used DTT in conjunction with glutathione had little or biological activity (Example 5, page 13, lines 24-32; page 14, lines 18-20). However, refolded in the glutathione redox system involved a slow dilution of the urea-solubilized material with a balanced redox buffer (page 13, lines 8-12), the same fusion protein was biologically active (page 14, lines 18-20). Thus, whether a refolded TGF-β fusion is active or not depends not only upon the structure of the fusion protein such as the leader sequence, but also the refolding conditions.

Accordingly, in view of various factors as noted above, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

(iii). Claims 6-9, 20, and 21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as

to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

Claim 6 is drawn to a latent TGF-β family member fusion protein, comprising a first TGF-β family proein C-terminal seven cysteine domain, comprising a finger 1 subdomain, a finger 2 subdomain, and a heel subdomain; and a cleavable leader sequence operably linked to said C-terminal domain wherein said cleavable leader sequence is selected from the group consisting of a leader sequence derived from a second TGF-β family protein, a metal-binding domain, a protein-binding domain, a ceramic-binding domain, a hydroxyapatite-binding domain and a collagen-binding domain; wherein said cleavable leader sequence inhibits the biological activity associated with said C-terminal domain; wherein said C-terminal domain becomes active upon cleavage of a part or all of said leader sequence; and wherein said latent protein is a refolded protein. Claims 7-9, 20, and 21 depend from claim 16. Thus, the

claims encompass a genus of cleavable sequences operably linked to a genus of TGF-β family protein C-terminal domains.

The specification discloses a fusion protein, H2440, which is a hexa-his tagged OP-1 (Fig. 7B). This protein was purified over copper IMAC resin, initially in its unfolded state, in the presence of urea. The folded fusion protein displayed little or no activity in a ROS assay, but was activated upon cleavage of the N-terminal non-morphogen peptide to yield an active C-terminal morphogen domain (page 77, the 1st paragraph). The specification also discloses that a modified morphogen containing a collagen binding domain (H2487, shown in Figure 7A) can be delivered in an inactive form to a desired tissue locus (e.g., a locus containing an implanted collagen matrix) and cleaved at that locus to produce an active morphogen (at page 79, the 2nd paragraph). However, the specification also states that the fusion protein of H2487 was successfully refolded and active in the ROS assay (page 77, lines 16-20), contradicting to the above disclosure at page 79, the 2nd paragraph of the specification. The specification further discloses numerous lead sequences that can be used to make a fusion protein (page 77, lines 7-8).

Such a disclosure does not adequately support the instantly claimed invention. The specification fails to disclose a representative number of species which would lead one skilled in the art to conclude that the Applicant was in possession of the claimed invention. The specification discloses that some N-terminal fusion protein monomers

disclosed in the instant disclosure do not form active homodimers without cleavage of the leader sequence (page 79, last paragraph). However, the specification does not provide description of the structural feature that makes a leader sequence inhibits the biological activity associated with a TGF-β family protein C-terminal domain and thus renders a TGF-β family member fusion protein latent. The specification does not disclose a latent fusion protein comprising a first TGF-β family protein C-terminal domain and a leader sequence derived from a second TGF-β family protein. The specification does not disclose a fusion TGF-β family protein wherein a part of the leader sequence is cleaved. Thus, the applicant was at most in possession of the latent fusion proteins, H2440 and H2487 shown in Fig. 3A and 3B. Moreover, the specification asserts that some N-terminal fusion protein monomers that do not form active homodimers without cleavage of the leader sequence form active heterodimers between those proteins and unmodified monomers of TGF-β family proteins (page 79, last paragraph). Therefore, the latent TGF-β family member fusion proteins are really limited to the latent TGF-β family member fusion protein homodimers.

Furthermore, the prior art teaches that the activities of the refolded proteins depend upon the refolding conditions (Hall et al., WO 96/39430, 12 December 1996; Nimni et al., U.S. Patent No. 6,352,972 B1). For example, Hall et al. teach that the refolded fusion protein comprising a His-tagged C-terminal active fragment of TGFβ1 under low concentrations of urea and DTT or a redox system used DTT in conjunction with glutathione had little or biological activity (Example 5, page 13, lines 24-32; page 14,

lines 18-20). However, refolded in the glutathione redox system involved a slow dilution of the urea-solubilized material with a balanced redox buffer (page 13, lines 8-12), the same fusion protein was biologically active (page 14, lines 18-20). Thus, whether a refolded TGF-β fusion is active or not depends not only upon the leader sequence, but also the refolding conditions and the formation of homodimers or heterodimers.

Accordingly, one skilled in the art would not recognize from the disclosure that the applicant was in possession of the instantly claimed latent TGF-β family member fusion proteins.

(iv). Response to Applicants' argument

Applicants argue that claim 6 has been amended to recite that the cleavable leader sequence is selected from the group consisting of a leader sequence derived from a second TGF-β family protein, a metal-binding domain, a protein-binding domain, a ceramic-binding domain, a hydroxyapatite-binding domain and a collagen-binding domain. Applicants argue that the specification provides adequate written description for claim 6 as amended. Applicants' argument has been fully considered, but is not deemed to be persuasive for the reasons set forth above.

Claim Rejections under 35 U.S.C. §102

(i). The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

(ii). Claims 6-8 and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Hall et al. (WO 96/39430, 12 December 1996).

Hall et al. teach a TGF-β fusion protein comprising a TGF-β1 active fragment (the C-terminal domain of TGF-β1) and a leader sequence. The leader sequence may comprise a purification tag, proteinase-sensitive linker sites and a protein binding domain such that the leader sequence may contain all or some of the following elements: purification tag:proteinase site: ECM binding site: proteinase site: TGF-β (page 4, the 2nd paragraph). Table 1 lists various TGF-β1 fusion proteins, such as a His-tagged C-terminal active fragment of TGFβ1 (Table I, lines 2; page 12, lines 26-28). Hall et al. teach that the refolded fusion protein under low concentrations o urea and DTT or a redox system used DTT in conjunction with glutathione had little or biological activity (Example 5, page 13, lines 24-32; page 14, lines 18-20). Since the fusion protein appears to satisfy the structural requirement, the additional properties recited in claims 6-8 are inherent to the structure of the fusion protein. Thus, the teachings of Hall et al. meet the limitations of claims 6-8 and 20.

(iii). Claims 6-8, 20, and 21 are rejected under 35 U.S.C. 102(e) as being anticipated by Nimni et al. (U.S. Patent No. 6,352,972 B1, March 5, 2002; 102(e): June 3, 1997).

Hall et al. teach a TGF-β fusion protein comprising a TGF-β1 active fragment (the C-terminal domain of TGF-β1) and a leader sequence. The leader sequence may comprise a purification tag, proteinase-sensitive linker sites and a protein binding domain such that the leader sequence may contain all or some of the following elements: purification tag:proteinase site: ECM binding site: proteinase site: TGF-β (page 4, the 2nd paragraph). Table 1 (column 5) lists various TGF-β1 fusion proteins, such as a His-tagged C-terminal active fragment of TGFβ1 (Table I, lines 2; page 10, lines 3-4). Hall et al. teach that the refolded fusion protein under low concentrations o urea and DTT or a redox system used DTT in conjunction with glutathione had little or biological activity (Example 5, column 10, lines 44-57; column 11, lines 6-8). Hall et al. teach a fusion protein comprising the active portion of BMP proteins, such as OP-1, also called BMP-7 (column 2, line 22; column 3, lines 13-18). Since the fusion protein appears to satisfy the structural requirement, the additional properties recited in claims 6-8 are inherent to the structure of the fusion protein. Thus, the teachings of Hall et al. meet the limitations of claims 6-8, 20, and 21.

Claim Objections

Claims 6-9 and 20 are objected to because they recite non-elected subject matter (TGF-β family proteins). Appropriate correction is required.

Conclusion

No claims are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ruixiang Li whose telephone number is (571) 272-0875. The examiner can normally be reached on Monday through Friday from 8:30 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, can be reached on (571) 272-0835. The fax number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, please contact the Electronic Business Center (EBC) at the toll-free phone number 866-217-9197.

/Ruixiang Li/

Primary Examiner, Art Unit 1646
January 12, 2009